AU-1652
THR-963

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Irritant Effects Of DU112307 (W.P. 25%) On Rabbit Eye Mucosa

Report No. 56645/18/73

Test Compound: DU112307 (W.P. 25%)
Batch No. 311301

Test Specie: New Zealand White Strain

Number of Rabbits: Eight Rabbits

Route of Administration: Instillation into eye

Dose: 1/10 ml DU112307 w.p. 25% in a concentration of 0.5 gm/ml in 0.9% ~~Nace~~ NaCl solution

Testing Laboratory: B.V. Philips - Duphar, Weesp, Holland

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Methodology: The testing procedure was according to FDA procedures published in the Federal Register 37 No. 83, April 1972.

Results: The report states that the test material had no irritation effect on the eye and associated tissues in the subsequent seven days post treatment.

Conclusion: DU1123307 w.p. 25% (0.5% gm/ml) was not irritating to the rabbit eye when tested according to the method of FDA published in the Federal Register 37 No. 83, April 1972 according to Dr. A. V. Eldik.

Validation: Invalid -- no animal test data submitted.

Section II - Vol. II of VII

Primary Skin Irritation Study

Test Compound: TH-6040 Technical

Test Specie: Albino rabbit

Number of Animals: Six rabbits

Route of Administration: Dermal

Dose: According to FHSLA protocol

Testing Laboratory: Harris Laboratories

Methodology: Protocol as described in "Regulations Under the Federal Hazardous Substances Labeling Act," Federal Register, August 12, 1961, Sec. 191.11

Results: No erythema, eschar or edema formation was noted at 24 or 72 hours post treatment.

Conclusion: When TH-6040 (Technical) was applied to the skin of rabbits as outlined in "Regulations Under The Federal Hazardous Substances Labeling Act," August 12, 1961, Sec. 191.11, no erythema, eschar or edema formation on abraded or intact skin was noted in any of the six rabbits either at 24 or 72 hours. TH-6040 (Technical) is not a primary skin irritant to the rabbit, when tested according to the above method.

Comment: Complete identification of test material is required.

Validation: Core - Guidelines.

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Primary Skin Irritation Study

Test Compound: TH6040 W-25 Wettable Powder

Test Specie: Albino Rabbits

Number of Animals: Six Rabbits

Route of Administration: Dermal

Dose: According to FHSCA Protocol

Testing Laboratory: Harris Laboratories
Lincoln, Nebraska

Methodology: Protocol as described in "Regulations Under the Federal Hazardous Substances Labeling Act" Federal Register, August 12, 1961, Sec. 191.11

Results: No erythema, eschar or edema formation was noted at 24 or 72 hours post treatment.

Conclusion: When TH-6040 wettable powder was applied to the skin of rabbit as in the method outlined in "Regulations Under The Federal Hazardous Substances Act," August 12, 1961, Sec. 191.11, no erythema, eschar or edema formation was noted on abraded or intact skin in any of the six rabbits either at 24 or 72 hours. TH-6040 W-25 wettable powder is not a primary skin irritant to the rabbit when tested according to the above method.

Comment: Complete identification of test material is required.

Validation: Core - Guidelines

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Section 13 - Vol. II of VII

Acute Toxicity Studies With
DU112307 (Technical) In Mice After
Intra-Peritoneal Administration

Report No. 56645/1/74

Test Compound: DU112307 technical product (Batch # 201252)

Test Specie: Swiss strain mice

Number of Animals: Ten mice, five males and five females/dose level, total 80 mice.

Route of Administration: Intraperitoneally

Doses: 2150; 1000; 464; 205; 100; 46.4; and 21.5 mg/kg

Testing Laboratory: B.V. Philips-Duphar, Weesp, Holland

Methodology: DU 112307 Technical was administered i.p. as a 25% PVP suspension in 0.9% saline solution to five male and five female mice per dose level. The doses were 2150, 1000, 464, 215, 100, 46.5 and 21.5 mg/kg mouse body weight. Controls were treated with vehicle. Animals were observed for signs of toxicity for 14 days subsequent to treatment.

Results: When DU 112307 (Technical) was administered i.p. to mice at doses up to 2,150 mg/kg, no mortality or signs of overt toxicity were noted in any of the mice during the fourteen days post treatment observation period.

Conclusion: There is no toxicity to mice when DU 112307 Technical is administered i.p. up to a dose of 2,150 mg/kg.

Validation: Invalid. No animal test data is available.

Comment: When TH6040 was administered i.p. in the mutagenicity study (IBT) at 2,000 mg/kg, hypoactivity was noted.

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Dietary Administration Of DU112307 to Male and Female Rats for 3 Months

Report # 56645/13A/73
Report # 56645/13B/73

Test Compound: DU112307 (Batch No. 201252)

Test Animals: Wistar Rats

Number of Animals: 60 males and 60 females

Route of Administration: Dietary

Doses: 0, 3.125, 12.5, 50 and 200 ppm

Testing Laboratory: Philips-Duphar, Weesp, Holland

Methodology: Sixty males and sixty female rats were divided into five groups. An additional 10 animals, 5 males and 5 females were placed in controls and again in the high dose level for serum for clinical chemistry analysis. The experiment lasted 3 months. The dose levels were 0, 3.125, 12.5, 50 and 200 ppm. Parameters monitored were clinical signs, body weight and food consumption, haematology, clinical chemistry, organ weights and gross and microscopic pathology.

Results: At seven weeks there was a gradual dose-related decrease in P.C.V. and hemoglobin in all female treated groups becoming statistically significant at the highest dose level.

At thirteen weeks, there was a dose-related decrease in R.B.C., P.C.V. and Hb in males becoming statistically significant at the highest dose level.

At seven weeks dealing with group mean values again, there was an increase in urea in males at the highest dose level and an increase in alkaline phosphatase over control values. Male rats at 13 weeks also showed an increase in S.G.O.T. and S.G.P.T. at the highest level. At 13 weeks female rats also showed a dose-related increase in S.G.P.T. and S.G.O.T.

Male rats showed a dose-related increase in absolute testes weight becoming statistically significant at the highest dose level. This same effect could be observed in adrenals in all treated groups.

Summary: The above-mentioned results show that certain hematolcgical and biochemical factors reflecting toxicity, while becoming statistically significant at higher dose levels, ~~over~~ the less show trends at all dose levels including the lowest dose level of 3.125 ppm.

The establishment of liver pathology at the 50 and 200 ppm dose level cannot be established at a no-effect dose level when even one animal out of nine shows the same pathology at the lowest dose level of 3.125 ppm.

The establishment of a no-effect dose level based on the histopathological findings of liver effects when no other tissues were examined at ~~any~~ each of the other dose levels is inappropriate.

Validation: Invalid.

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DU112307
Toxicity in Repeated Dietary
Administration to Beagle Dogs
(Repeated Administration for 13 weeks)

Report No. 169/74157

Test Compound: DU112307 (Batch # P7227)

Test Species: Pure-bred Beagle dogs

Number of Animals: 5 groups at 3 males and 3 females/group.

Route of Administration: Dietary

Doses and duration: 0, 10, 20, 40, 160 ppm for 13 weeks.

Testing Laboratory: Huntingdon Research Center
Hungtindon, England

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Methodology: Thirty pure bred beagles, fifteen males and fifteen females were equally divided into 5 groups with 3 males and 3 females per group. The dose levels were 0, 10, 20, 40, 160 ppm for 13 weeks. Four hundred grams of dog food was offered each day to each dog. Amounts not eaten were recorded. A supplement of milk was included and water was "ad lib." Clinical signs, body weights, food and water consumption were periodically recorded. Ophthalmoscopic examination was conducted at the beginning of testing at 6 and 12 weeks into the study. Laboratory investigations included haematology, biochemistry, urinalysis and histopathology.

Results: The actual consumption of test compound in the 0, 10, 20, 40, 160 ppm dose levels was 0, 0.42 mg/kg/day, 0.84/mg/kg/day, 1.64 mg/kg/day and 6.24 mg/kg/day dog body weight. During a test period of 13 weeks, there were no mortalities and no clinical signs were observed. Body weight gains appeared satisfactory with the exception of one control dog. This dog had a condition of hydrocephalus.

Opthalmoscopy revealed no abnormalities in the eyes of all dogs.

At two weeks into the study, haematology and biochemistry appear to be within normal limits.

At four weeks one dog at 160 ppm dose level had a decrease in RBC. Increased SAP values were noted for dog #315 (40 ppm) and 319 and 322 (160 ppm). Three dogs, 319 , 320 and 322 (100 ppm) showed elevated SGPT values. At six weeks the RBC counts were significantly lower at 160 ppm. Methaemoglobinemia was greater in the high test group than controls but only those two dose levels were tested for methemoglobinemia. The report states that abnormal haemoglobin pigments were observed at 160 ppm. It is unknown whether these abnormal blood pigments exist at the lower dose levels. These abnormal pigments are in addition to sulphaemoglobin. An increase in SAP values at 40 and 160 ppm and a dose related increase in SGPT starting at the lowest dose level of 10 ppm. At 12 weeks, haematological values appear to be within normal limits. Methemoglobineamia is present to an appreciable degree only in one dog at 160 ppm dose level. While plasma free haemoglobin seemed to increase in some groups, there were no dose related effects. At the end of the experiment, no histological abnormalties were seen which could be related to test compound administration.

Validation: Core-Guidelines

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Section 17 - Vol. III of VII

PH 60-40 Excretion Of Radioactivity And Metabolic Patterns In Rats Following Oral Administration

Report No. 56654/20/74

Test Compound: PH60-40

Testing Laboratory: B.V. Philips - Duphar

Purpose: To determine metabolic patterns following oral administration of PH60-40

Methodology: PH60-40 was labelled in various parts of the molecule with C^{14} and H^3. Urine, bile, feces and air were monitored analytically to detect their presence.

Results: The poor recoveries of the labelled moieties in these excretion fluids failed to indicate a metabolic pattern.

Comment: A more sensitive technique is required to assess excretion patterns in rats. Elucidation is needed concerning differences in excretion patterns between male and female rats or whether the results are artifacts.

Validation: Invalid - the experiment did not achieve its intended purpose.

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Section 18 - Vol. III of VII

Diflubenzuron (PH 60-40)
Balance Studies In the Rat

Report No. 56654/22/75

Test Compound: PH 60-40

Purpose: 1. To obtain consistent recoveries of labelled material.

2. To identify the metabolites.

Methodology: As in experiment Section 17 - # 56654/20/74

Results: It was established that about 50% of the dose of test material was absorbed from the intestines. About 75-80% of the urinary metabolites were established, as far as the benzoyl moity or the parent compound was concerned. About one-half of this amount was identified as 2,6 difluorobenzoic and not much could be stated about the 4-chlorophenylurea moiety.

Validation: Supplementary data.

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Section 19 - Vol III of VII

Treatment of Chickens With [^{14}C]TH-6040

Treatment of Female Poland China-Duroc Cross Pig With [^{14}C]TH-6040

These experiments are within the competancy of the Chemistry Branch with the exception of the pathology reports on the chicken and pigs.

Results: Pathology report # 427186 on the chickens states that 4 mature chickens had been fed each a single dose of TH 6040 at 5 mg/kg. The histologic examination diagnosed fatty metamorphosis of the liver. The birds were necropsied 12 days after dosage.

Results: Pathology report # 387765 on Rhode Island Red X Barred Rock Cross chickens states that histologic examination showed "almost all the liver cell nuclei were undergoing karyorrhexis". The diagnosis was "Karyorrhexis, liver cells, marked".

Note: Karyorrhexis constitutes the fragmentation of nuclei into chromatin particles which scatter in the cytoplasm.

Results: Pathology report # 387824 on a pig fed TH 6040 at 5 mg/kg in a single dose 10 days prior to necropsy-- diagnosis, "Diffuse changes of a mild fatty metamorphosis."

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A Preliminary Report On The Metabolic Fate of Dimilin - ^{14}C

In A Lactating Cow

This review is within the competency and jurisdiction of the Chemistry Branch.

Comment: TB takes note however that radioactive carbon residues in tissues of a lactating cow 7 days after oral treatment with Dimilin ^{14}C at 10 mg/kg shows liver to have 2.9 ppm Dimilin equivalents.

TH-6040

MILK AND TISSUE RESIDUE STUDY IN DAIRY COWS

This review is within the competency and jurisdiction of the Chemistry Branch.

Section 22 - Vol. III of VII

Isolation, Purification and Identification of the TH 6040 and Its Metabolites From The Liver Of The Cow Exposed to ^{14}C TH 6040

This review is within the competency and jurisdiction of the Chemistry Branch. However, TB notes the following results which may impinge upon the evaluation of safety.

Results: The following figure 1 presents the schematic outline of the degradation of TH 6040 in bovine liver when the cow was fed TH 6040 at 250 ppm in the diet for seven consecutive days.

Figure 1: Proposed Metabolism Scheme for T.H. 6040 in Bovine Liver

Cannon Laboratories, Inc.

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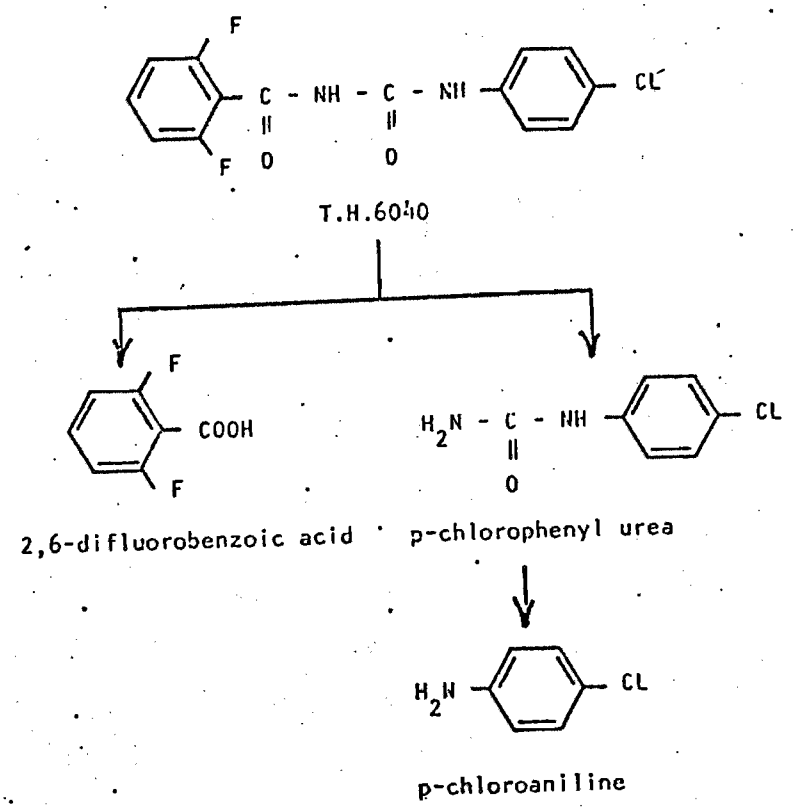
FIGURE 1: PROPOSED METABOLISM SCHEME FOR T.H.6040 IN BOVINE LIVER



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T.H. 6040 Egg And Tissue
Residue Study in Poultry

This review is within the competency and jurisdiction of the Chemistry Branch.

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Isolation, Purification And Identification Of T.H. 6040 And Its Metabolites From Tissues And Eggs of Poultry Exposed To ^{14}C-T.H. 6040

This review is within the competency of the Chemistry Branch.

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Section 25 - Vol. III of VII

The Administration Of TH-6040 At A Dose Level of 300 PPM, To a Steer For 14 Consecutive Days

Lab. No. 5E-8153

Test Compound: Dimilin-W-25 (TH-6040)

Test Specie: One Steer

Route of Administration: Capsule

Duration of Study: 14 days

Dose: 300 ppm

Test Laboratory: Cannon Laboratories, Inc.
Reading, Pennsylvania

Sponsor: Thompson-Hayward Chemical Co.

Methodology: A steer (no weight given) was administered Dimilin W-25 (TH-6040) at 300 ppm for 14 consecutive days. The report states that the steer was dosed by capsule at 9:00 A.M. each day. After 14 consecutive doses, the animal was sacrificed and a detailed gross observation was made to the liver, kidney, brain, heart, lungs, stomach and GI tract. The report states that those organs were preserved in 10% buffered formalin and submitted for histopathological evaluation.

Results: There was a slight diminution in food and water consumption early in the experiment but soon returned to normal. Gross pathology examination showed all organs to be normal. The histopathology report states that the tissues examined were heart, kidney, bile duct and liver. Foci of chrome inflammation were found in heart and liver.

Comment: Clarification is needed:

(1) The report states that liver, kidney, brain, heart, lungs stomach, GI tract were submitted for histopathological examination yet, the tissues examined microscopically were only heart, kidney, bile duct and liver.

(2) The protocol states that the steer was dosed at 300 ppm yet the protocol also states that the test material was given in a capsule.

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(3) The protocol states that one steer was treated but results were on on two steers, one treated and one control.

(4) No data is available on food, water consumption on the control steer.

(5) Dimilin W-25 is equated to TH-6040. Is Dimilin W-25 a 25% wettable powder?

Validation: Invalid, unless clarification is forthcoming concerning questions raised under comments.

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Section 26 - Vol. III of VII

Effect of Repeated Applications Of DU 112307 To the Skin of Rabbits For Three Weeks

Report # PDR 146/73845

Test Material: DU112307 (Batch No. P7131)

Test Specie: New Zealand White Rabbits

Number of Animals: 60 rabbits, 30 males, 30 females

Route of Administration: Dermal

Dose: 1.5 ml/kg/day of DU112307-23% to group 3, group 4

1.5 ml/kg/day of DU112307-70% of group 5, group 6.

Testing Laboratory: Huntingdon Research Center
Huntingdon, England

Sponsor: M.V. Philips-Duphar, Weesp, Holland

Methodology: Sixty New Zealand rabbits, were randomly divided into 6 groups, 5 males and 5 females/group. All rabbits were acclimatized, weighed, earmarked. Rabbits were housed individually in metal cages with wire mesh floors, and had free access to water and standard rabbit diet medicated with 0.1% formosulphathiazole. Hair was clipped from trunks exposing an area about 5% of total body surface. Rabbits in groups 2, 4 and 6 were abraded while rabbits in groups 1, 3, 5 were non-abraded. Each rabbit was supplied with an "Elizabethan" collar to avoid oral ingestion of test materials. Test material was applied at 1.5 ml/kg/~~day~~ five days per week for three weeks. Controls received vehicle, gum tragacanth 0.5% alone. Along with recording ~~gain~~ reactions, clinical signs, food consumption, body weight, hematology, blood chemistry, and ophthalmological data were recorded. Some organ weights were taken and tissues were preserved in buffered formaldehyde.

Results: Sporadic transient erythema was observed in all groups showing nothing remarkable that might be attributed to DU112307. DU112307 at 70% did show a more marked erythema (grade 2) but still a transient effect.

There were no signs of toxicity as might be observed clinically in any of the rabbits.

Weight gains were depressed in rabbits treated with DU112307 at 70% especially in the females.

Hematologically, there was seen a tendency to higher reticulocyte counts in both sexes with both the 23% solution as well as the 70% solution.

Blood chemistry demonstrated very high methemoglobinemia values in all DU112307 treated groups but especially in the males. Control males showed 0.1 g % methemoglobinemia while abraded rabbits in the 23% and 70% groups showed 1.6 g % and 1.3 g % methemoglobinemia respectively. The report states that the blood from all groups had an "unusual dark colouration," probably due to methemoglobin and other unidentified blood pigments.

Eye examinations did not detect any abnormalties.

Macroscopic examinations did not reveal anything unusual or attributable to DU112307 treatment.

Organ weight analyses showed some variations but values remained within normal range.

Microscopic examination of tissues showed nothing remarkable except that "peribronchial lymphoid hyperplasia was seen in the majority of animals examined and was associated with perivascular and subplural aggregations of lymphocytes in many instances."

Conclusions: DU112307 produces methemoglobinemia in New Zealand rabbits when applied at 1.5 ml/kg at both 23% and 72% concentrations.

Comments: The report states that other blood pigments were present. These were not identified.

There is no data to show whether this methemoglobinemia is transitory or permanent in rabbits.

Histopathology was done only on groups 2, 5 and 6.

Peribronchial lymphoid hyperplasia would appear to be common to all the animals both in group 2 controls and in group 5 and 6 treated. Since white blood cell counts were well within normal range, it is questionable whether the lymphoid hyperplasia in the lungs can be reflective of a generalized inflammatory condition.

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Effect of Repeated Applications Of DU112307 To the Skin of Rabbits For Three Weeks

Report # PDR 200/7485

Test Compound: DU112307 (Batch # 405093)

Test Animals: New Zealand Winter Rabbits

Number of Animals: 80 Rabbits, 40 males and 40 Females

Route of Administration: Dermal

Dose: 1.5 ml/kg/day of DU112307 in gum tragacanth. Solutions of DU112307 used were 4.64% , 10%, 21.5%

Testing Laboratory: Huntingdon Research Center
Huntingdon, England

Sponsor: M. V. Philips-Duphar, Weesp, Holland

Methodology: Same as in Section 26 - Vol. III of VII.

Results: Sporadically, a case of mild erythema grade 1 was reported in some rabbits. These local skin irritations appeared transitory in most cases and are not related to treatment.

No signs of toxicity could be observed clinically.

Food consumption, body weight data varied sporadically and would not be related to treatment.

~~Hematology~~ other observations appeared within normal limits.

Opthalmoscopy showed no effects which could be related to toxicity.

Blood chemistry appeared sound with the exception of methemoglobinema and sulphemia globinemia. As the dose levels rise so do the levels of these parameters.

Macroscopic and microscopic pathology showed no signs of toxicity due to DU112307.

Conclusion; Methemoglobinema is induced by DU112307 dermally on the intact skin of male New Zealand rabbits down to the lowest rate

of application 1.5 ml/kg at 4.64%. Increased effects are observed in the males at the median and highest dose levels.

The females ~~can~~ show these effects beginning at 4.64% ~~to~~ concentration through to the median and highest dose level.

Comments: Clarification is needed:

The experimental procedure states that 60 New Zealand white rabbits were obtained for the experiment and 80 rabbits were reported in the experiment.

Validation: Core-Guidelines - tentative

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Subacute Inhalation Toxicity To The Rat Of DU 112307 W.O. 25%
Insecticide Powder

PDR 148/73848
HRC Rysit 4920/72/355

Test Compound: DU 112307 (PH 60-40 w.p. 25%) # 304051

Test Specie: Albino Rat-Sprague Dawley CD1 (Grade IV)

Number of Rates: Twenty males and twenty females
Five males and five females per dose level
Five males and five females controls

Route of Administration: Inhalation

Dose and Duration of Exposure: Exposure periods 1 hour
Five days per week
Three weeks
Nominal concentrations 0.5, 5.0, and 50 mg/liter air

Testing Laboratory: Huntingdon Research Center, Huntindon, England

Sponsor: N.V. Philips-Duphar, Weesp, Holland

Petition: Thompson Hayward Chemical Company

Methodolgy: A wright dust generator and/or a Timbrell dust generator was used to aerosolize DU 112307 wp. 25% into chambers at a rate to offer nominal concentrations of 0.5, 5.0, 50 mg of test material per liter of air. The dust was generated into chambers for one hour per day, five days per week for three weeks. The chamber contained one group of ten rats, per test period, with wire mesh separating each rat. Control group was treated only with air. Actual concentrations of dust were calculated by gravimentric sampling. Mean gravimentric findings for the three dose levels were 0.61 mg/liter air, 0.351 mg/liter air and 3.29 mg/liter air for the nominal concentrations of 0.5, 5 and 50 mg/liter of air, respectively. Particles ~~scopes~~ sizes were in the respirable range. Clearance temperature was 24°c + 2°c and humdity 35% + 3%.

Results: No clinical signs were observed in animals exposed to 0.5 mg/liter test material in air while blinking, sneezing and laboured breathing were observed at the higher dose levels. Nasal secretions were noted at 50 mg/liter dose level but all animals appeared to be normal once removed from aerosolized dust.

Mean body weights were like controls. Food and water consumption appeared normal.

Urinary sediments showed RBC present at the third week from male rats in the three test groups, but not in controls. Haematological parameters varied in the three groups but variations did not reflect treatment related effects.

Macroscopic and microscopic pathology did not reveal anything unusual for this strain of rat.

Organ weights showed a dose related increase in spleen weights (except females at 0.5 mg/liter) for both sexes in the test groups with statistical significance for both sexes at the highest dose level and also for females at the median dose level. No deaths were reported throughout the study.

Comments: Two dust generating machines, the Wright and Timbrell dust generators were mentioned as the means of generating dust. No mention is made which one generator was used or whether both were used in this inhalation experiment.

Sections of tissues were taken for histopathology examination from groups 1 (controls) and group 4 (high dose level) but no statement was made as to exactly what tissues were taken routinely for study from each animal.

DU 112307 is 25% Dimilin. A statement is needed concerning the contents of the 75% remaining formulation.

Comments: With the increases observed in spleen weights in this experiment, it is deemed necessary that histopathology be employed to determine the cause of the increase weights. Not one animal spleen was microscopically examined and reported.
There is a dose related increase in SGPT in male rats also.

Conclusion: Test material must be completely identified in report. The effects on spleen weight as might be determined by histological examination need to be known before any conclusion can be reached in regards to the inhalation effects of DU 112307 w.p. on Sprague Dawley rats at the above stated concentrations and for this time schedual.

Validation: Supplementary

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